

12

EUROPEAN PATENT APPLICATION

21 Application number: 79301446.5

51 Int. Cl.3: A 61 K 7/06

22 Date of filing: 20.07.79

30 Priority: 21.07.78 GB 3072578

71 Applicant: Unilever N.V., P.O. Box 760  
Burgemeester 's Jacobplein 1, NL-3000 DK  
Rotterdam (NL)  
84 Designated Contracting States: BE CH DE FR IT NL SE  
AT

43 Date of publication of application: 20.02.80  
Bulletin 80/4

72 Inventor: Mathur, Girish Prasad, 33 Landmark, 175  
Carter Road, Bandra, Bombay 400 040 (IN)  
Inventor: Anavkar, Arun Shantaram, 13 Alice Court,  
Monghal Lane Behind Mahin P.O., Mahim,  
Bombay 400 016 (IN)  
Inventor: Menon, Kuruvakkat Kochu Govind, 6 Kamani  
House, Peddar Road, Bombay 400 026 (IN)

84 Designated Contracting States: AT BE CH DE FR GB IT  
NL SE

71 Applicant: Unilever Limited, Unilever House,  
Blackfriars P.O.Box 68, London E.C.4 (GB)  
84 Designated Contracting States: GB

74 Representative: Tonge, Robert James et al, Unilever  
Limited Patent Division PO Box 31 Salisbury Square  
House Salisbury Square, London EC4 4AN (GB)

54 Hair treatment composition and method.

57 A hair and scalp treatment composition comprises a  
diazole such as imidazole and histidine or histidine deriva-  
tives, and a mono basic acid such as methionine or p-amino  
benzoic acid, together with a physiologically acceptable  
carrier. Optionally, folic acid can also be included in the  
composition.

EP 0 008 171  
A1

see front page

The invention relates to novel compositions which are capable of stimulating hair growth, and/or restoring hair growth, and/or reducing hair loss in human beings.

5        Except for the palms and soles, the entire skin surface of human beings is normally hirsute. Hair grows from the cell divisions of matrix cells in a region known as the bulb. In all hairy animals (with the possible exception of merino sheep and poodle dogs) hair follicles  
10      show cyclic activity. In such species as mice and rats all hairs are in the same state of activity, and their cyclic changes are synchronised. However, in human beings and in animals such as guinea pigs, the cycle of each follicle occurs independently from those of the neighbouring follicles and show a mosaic pattern.  
15

The hair cycle is divided into three stages : anagen (growing or active stage), catagen (regressive stage) and telogen (resting stage). The rate of growth of the hair varies from species to species and, in man, from region  
20      to region. During human life hair cycles are reproduced repeatedly. The length of hair cycle also varies from species to species and there are regional variations as well.

Most human body hairs grow to predictable lengths  
25      peculiar to the body area and to the individual. Like all hairs they undergo periodic shedding and are replaced by other hairs of the same length. The number of hairs in

men and women are nearly the same. Of 90,000-100,000 scalp hairs in humans, irrespective of sex, about 90% are in growing (anagen) stage and about 10% in resting (telogen) stage. Human hair grows at the rate of about 5 0.3-0.4 mm per day but this is influenced by many factors.

Scalp hair in humans has been valued for its adornment value since antiquity. Alopecia or scalp hair loss in man usually occurs with senility. However, chronic hair losses in both young males and females have 10 been observed during or after psychological stress, high fever, surgical shock, treatment by antibiotics, drugs (e.g. methotrexate, 6-mercaptopurine, actinomycin D, aminopterin, 5-fluorouracil, cyclophosphamid, etc.), X-ray treatment, after pregnancy or after discontinuation 15 of oral contraceptives, and, even during strict diet control. Although luxuriant growth of hair is normal and natural in most people, many people use hair tonic to promote healthy hair growth and reduce falling hair. Many such hair tonics contain a variety of natural substances, 20 e.g. oil of cade, capsicum extract, cantharidin, jaborandi leaf extract (contains alkaloid pilocarpine), oils from berries of Emblica officinalis Gaertn, juice of flowers of Hibiscus rosa sinesis, umblicial cord and placental extract, extract of tea and coffee, etc. 25 Many chemical compounds like sulphur-containing amino acids, cysteine or thiazolidine-4-carboxylic acid, N-acetyl homocysteine thiolactone, camphor, quinine,

inositol, hydrocortisone, pantothenic acid, pantothenol, linoleic acid, arachidonic acid, etc., have all been claimed as useful ingredients for hair tonics.

The biological mechanisms regulating proliferation and differentiation of hair follicular cells are not fully understood and little is known about the cause of alopecia. Our studies suggest that proper balance of cyclic adenosine-3',5'-monophosphate (cAMP) and cyclic guanosine-3',5'-monophosphate (cGMP) in hair bulb is one of the important factors in controlling follicular activity. Imbalance of hair bulb cAMP and cGMP can result in increased hair loss, ultimately leading to alopecia. We have now found that topical application of imidazole and its derivatives like histidine, methionine, folic acid and p-aminobenzoic acid (PABA) tend to stimulate hair growth in model test systems. We have also found that topical applications of cocktails of imidazole or its derivatives like histidine, with methionine or PABA, and with methionine + PABA, are effective in stimulating hair growth and in increasing hair diameters.

The object of this invention is to provide novel compositions which stimulate hair growth and/or reduce falling hair. The invention accordingly provides a hair and scalp treatment composition comprising a diazole chosen from imidazole, histidine and its salts and esters and mixtures thereof; and a monobasic acid chosen from methionine, p-aminobenzoic acid and their salts and esters, and mixtures thereof, together with a physiologically acceptable carrier.

The composition can also optionally comprise folic acid which has been shown to provide a further stimulus to hair growth and/or regrowth.

The composition can furthermore optionally comprise  
5 inositol, zinc or magnesium compounds such as zinc oxide and zinc sulphate or magnesium sulphate and magnesium stearate or mixtures thereof which are believed to further contribute to an improvement in the general health of the hair and scalp.

10 The amounts of substances, as hereinbefore defined which, when present, can be employed in the composition are as follows:

	Imidazole	from 0.1 to 5.0%, preferably from 1.0 to 3.0% by weight
15	Histidine, salts or esters thereof	from 0.1 to 10.0%, preferably from 0.2 to 3.0% by weight
	Folic acid, salts or esters thereof	from 0.1 to 5.0%, preferably from 0.2 to 2.0% by weight
20	Methionine, salts or esters thereof	from 0.1 to 5.0%, preferably from 0.2 to 3.0% by weight
	p-aminobenzoic acid, salts or esters thereof	from 0.1 to 5.0%, preferably from 0.2 to 3.0% by weight
	Myo-inositol	from 0.1 to 5.0%, preferably from 0.2 to 3.0% by weight
25	Zinc oxide or sulphate	from 0.1 to 1.5%, preferably from 0.1 to 0.6% by weight
	Magnesium sulphate or stearate	from 0.1 to 1.5%, preferably from 0.1 to 0.6% by weight
30	Soya- or egg-lecithin	from 0.1 to 5%, preferably from 0.1 to 1% by weight

The preferred form of histidine, when employed, is the salt L-histidine monohydrochloride. The preferred form of methionine, when employed, is the isomer DL-methionine.

The composition according to the invention also 5 comprises a physiologically acceptable carrier, the nature of which is unimportant, provided that it is safe in use and that it does not diminish the effectiveness of the active ingredients. Examples of physiologically acceptable carriers are oils, fats, phospholipids such as lecithin, 10 certain fatty acids, and long chain alcohols such as cetyl alcohol, usually in the form of an emulsion or alcoholic suspension or solution. The scope of this invention is however not limited to these examples of carriers.

The composition of the invention may be in any of the 15 physical forms which are suitable for cosmetic application to the scalp, for example hair creams, pourable emulsion hair dressings and alcoholic hair lotions.

The invention will now be described by way of the following examples of hair creams, pourable emulsion hair 20 dressings and alcoholic lotions found useful in stimulating hair growth and/or reducing falling hair in human subjects.

	<u>HAIR CREAM</u>				
	<u>Example 1</u>	<u>Example 2</u>	<u>Example 3</u>	<u>Example 4</u>	<u>Example 5</u>
1. Mineral oil	-	32.000	-	-	-
2. Coconut oil	40.000	-	27.00	40.00	27.000
3. Petroleum Jelly	-	5.000	10.00	-	10.000
4. Beeswax	2.300	2.800	2.300	2.300	2.300
5. Stearic acid	2.225	2.225	2.225	2.225	2.225
A 6. Cetyl alcohol	0.200	0.200	0.200	0.200	0.200
7. Nipagin M	0.100	0.100	0.100	0.100	0.100
8. BHA	0.100	0.100	0.100	0.100	0.100
9. Lanolin	0.300	0.300	0.300	0.300	0.300
10. Egg lecithin	0.500	0.500	0.500	0.500	0.500
11. Arlacel-83	0.100	0.100	0.100	0.100	0.100
12. Magnesium sulphate	0.800	0.600	0.800	0.800	0.800
B 13. Zinc sulphate	0.400	0.300	0.400	0.400	0.400
15					

## HAND CREAM (CONTINUED)

		Example 1	Example 2	Example 3	Example 4	Example 5
	14. Imidazole	3.00	-	-	-	-
	15. Histidine	-	1.00	2.00	1.50	4.0
5	16. Methionine	1.00	3.00	-	0.5	1.0
C	17. P-amino benzoic acid	0.50	1.00	2.00	1.5	-
	18. Folic acid	1.00	2.00	1.00	2.0	0.5
	19. Inositol	0.50	2.00	-	1.0	2.0
10	20. NaOH	to pH 6.5-7.5				
D(	Lime water	14.625	14.625	14.625	14.625	14.625
	Perfume	0.500	0.500	0.500	0.500	0.500
	Distilled water	to 100				

Method of Preparation of Hair Cream

Step I - Mix the ingredients of A and heat to 50-60°C  
in a water bath.

5 II - Dissolve components of part B in 5-10 ml of  
water.

III - Dissolve components of C in 25-30 ml of  
distilled water.

10 IV - Heat separately A,C&D to 50-60°C. First add  
A to D with constant stirring. After the  
mixing is complete then add C to this mixture  
with stirring. Finally add the solution of  
components of B to the mixture with stirring.  
Complete the preparation with addition of  
perfume and remaining water. Homogenise the  
15 mixture to get a satisfactory hair dressing.

EMULSION HAIR DRESSING

		<u>Example 6</u>	<u>Example 7</u>	<u>Example 8</u>
	1. Mineral oil	19.50	18.00	19.50
	2. Isopropyl myristate	1.00	1.00	1.00
5	3. Cetyl alcohol	1.20	-	1.20
	4. Emulsol TK	2.00	-	2.00
	5. Arlacel-83	1.00	1.00	1.00
	6. Gelatin	0.50	-	0.50
	7. Polyvinyl pyrrolidone	-	2.00	-
10	8. Glycerol	-	5.00	-
	9. Stearic acid	-	2.00	-
	10. Lanolin	-	1.50	-
	11. Histidine	2.00	2.00	4.00
	12. Methionine	0.50	0.50	0.50
15	13. p-Aminobenzoic acid	1.50	1.00	0.8
	14. Folic acid	1.00	0.50	0.50
	15. Inositol	1.00	1.50	1.00
	16. Magnesium sulphate	0.20	0.20	0.20
	17. Zinc sulphate	0.40	0.40	0.40
20	18. Egg lecithin	0.50	0.50	0.50
	19. NaOH	to pH 6.5-7.5	to pH 6.5-7.5	to pH 6.5-7.5
	20. Methyl p-hydroxy benzoate	0.10	0.10	0.10
25	21. Perfume	0.50	0.50	0.50
	22. Distilled water	to 100	to 100	to 100

Method of preparation of pourable emulsion hair dressing

I - Oil phase:

Heat ingredients 1,2,3,4,5,9,10,18,20,21 to 50-60<sup>0</sup>C.

II - Aqueous phase A:

5 Make a slurry of ingredients 6,11,12,13,14,15 and to this add sufficient amount of NaOH to bring the pH to 6.5-7.5 when a clear solution will be formed. Heat the solution to 50-60<sup>0</sup>C.

III - Aqueous phase B:

10 Dissolve ingredients 7,8,16 and 17 in a small amount of water and heat to 50-60<sup>0</sup>C.

First mix the oil phase and aqueous phase A with vigorous stirring. To this mixture add aqueous phase B and homogenise several times.

ALCOHOL BASED LOTION

		<u>Example 9</u>	<u>Example 10</u>	<u>Example 11</u>
	1. Isopropyl myristate	2.0	1.0	1.0
	2. Tween-20	1.0	1.0	1.0
5	3. Alcohol	15.0	10.0	10.0
	4. Isopropyl alcohol	-	5.0	5.0
	5. Polyvinyl pyrrolidone	0.5	0.5	0.5
	6. Bronidiol	0.1	0.1	0.1
	7. Histidine	2.0	1.5	2.5
10	8. PABA	1.0	1.5	0.9
	9. Methionine	0.1	0.2	1.0
	10. Folic acid	0.3	-	0.2
	11. Inositol	0.5	0.5	0.5
15	12. NaOH	to pH 6.5-7.5	to pH 6.5-7.5	to pH 6.5-7.5
	13. Perfume	0.5	0.5	0.5
	14. Distilled water	to 100	to 100	to 100

Method of preparation of lotion

Prepare an aqueous slurry of ingredients 5 to 11.

20 To this add sufficient 20% aqueous solution of NaOH to bring pH to 6.5-7.5 thus obtaining a clear solution. To this solution add an aqueous alcoholic solution containing ingredients 1,2,4 and perfume to produce an alcoholic lotion.

25 The compositions as described in each of Examples 1 to 11 will significantly increase or improve hair growth

or hair regrowth when applied to the hair and scalp of male subjects showing male pattern baldness.

Example 12

This example describes the invention in terms of a 5 hair tonic formulation which was applied during the course of a clinical trial to the hair and scalp of male human subjects who exhibited varying degrees of baldness.

Hair tonic formulation

The hair tonic formulation employed in the clinical 10 trial was a coconut oil based hair cream which contained the following ingredients:

	<u>% w/w</u>
Coconut oil	40.000
Bees wax	2.300
Stearic acid	2.225
5 Cetyl alcohol	0.200
Lanolin	0.300
Nipagin	0.100
Butyl hydroxyanisole	0.100
Egg lecithin	0.500
10 Arlacel - 83	0.200
Magnesium sulphate, 7H <sub>2</sub> O	0.510
Zinc sulphate	0.440
L-Histidine monohydrochloride	5.000
DL-Methionine	0.500
15 P-Aminobenzoic acid	1.000
Folic acid	0.500
Sodium hydroxide	1.000
Perfume	0.500
Distilled water	30.000
20 Lime water	<u>14.625</u>
	<u>100.000</u>

Subjects

22 male subjects took part in the clinical trial.  
Each subject either had marked frontal baldness with a  
noticeable bald patch on the scalp, or showed only  
5 receding hair line typical of the onset of male pattern  
baldness.

Test design

Each subject was asked to collect daily the hairs lost  
by combing. The basal daily hair loss value was determined  
10 for each subject for 30 days before the start of the trial  
with the hair tonic. The subjects were then given a tube  
containing about 20g hair tonic cream, and instructed to  
apply it once or twice a day with massage. Each subject  
was required to recover the hair lost daily by combing  
15 and a number of hairs lost before and after use of the  
cream was recorded.

Hair diameter

In the case of 16 subjects, the hair diameter was  
determined on the hairs collected before use and 6 months  
20 after use of the hair tonic cream. The hair diameter was  
measured from the hair bulb at 1 mm intervals up to a  
distance of about 10 mm. It was observed that from 4 to  
6 mm from the hair bulb along the hair shaft, the diameter  
was essentially constant. Hair diameter was accordingly  
25 measured at 6 mm from the hair bulb and an average value  
for the hair diameter was calculated in the case of each  
subject.

Results

From an observation of the median daily hair loss of all the subjects both before and after use of the hair tonic, a general decrease in hair loss

5 became apparent after 3 months' use of the hair tonic. The results were analysed statistically and it was shown that there was a significant reduction in daily hair loss up to the end of the trial which was 12 months from the first application of the hair tonic.

10 The head of each subject was photographed at intervals during the trial, and new hair growth was observed in the bald patches of most of those subjects who had bald patches at the commencement of the trial.

15 Of the 16 subjects whose hair diameter had been measured during the course of the trial, a statistically significant increase in hair diameter was observed after application of the hair tonic.

Conclusion

The results of the clinical trial showed that 20 regular use of the hair tonic cream according to the invention reduced hair loss, stimulated new growth and tended to increase hair diameter. These effects were noticeable after 3 months' application of the hair tonic cream and further improvements were noted up to 12 months 25 which marked the conclusion of the trial.

\*\*\*

CLAIMS:

1. A hair and scalp treatment composition, characterised in that it comprises a diazole chosen from imidazole, and histidine and its salts and esters, and mixtures thereof; and a monobasic acid chosen from methionine, p-aminobenzoic acid and their salts and esters and mixtures thereof, together with a physiologically acceptable carrier.
2. A composition according to claim 1, characterised in that the imidazole forms from 0.1 to 5% by weight of the composition.
3. A composition according to claim 1, characterised in that it comprises histidine, methionine and p-aminobenzoic acid.
4. A composition according to claim 1, 2 or 3, characterised in that the histidine is L-histidine.
5. A composition according to any preceding claim, in which histidine forms from 0.1 to 10% by weight of the composition.

6. A composition according to claim 1 or 3, characterised in that the methionine is dl-methionine.

7. A composition according to claims 1,3 or 6, characterised in that the methionine forms from 0.1 to 5% by weight of the composition.

8. A composition according to any preceding claim, characterised in that the p-aminobenzoic acid forms from 0.1 to 5% by weight of the composition.

9. A composition according to any preceding claim, characterised in that it additionally comprises folic acid.

10. A composition according to claim 9, characterised in that the folic acid forms from 0.1 to 5% by weight of the composition.

11. A composition according to any preceding claim and substantially as described in any of the Examples.

12. A method of treating human hair, characterised in that it comprises applying to the hair and/or scalp a composition as claimed in any preceding claim.



DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 1)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	<p><u>GB - A - 1 408 036</u> (TREUHANDVER-EINIGUNG)</p> <p>* Page 2, line 33; page 3, line 11, 42-45; claims 1,14,28 *</p> <p>--</p>	1,3,4	<b>A 61 K 7/06</b>
A	<p><u>FR - A - 1 418 905</u> (I. KAWAKAMI)</p> <p>* Abstract 1°,4° *</p> <p>--</p>	1,2	
A	<p><u>GB - A - 1 126 018</u> (H.W. KUGELMANN)</p> <p>* Claims 4,5,6,8 *</p> <p>--</p>	1,3	<b>TECHNICAL FIELDS SEARCHED (Int.Cl. 1)</b>
A	<p><u>DE - B - 1 017 331</u> (WELLA)</p> <p>* Example; claim *</p> <p>--</p>	1,8	<b>A 61 K 7/06</b>
A	<p><u>DE - A - 2 242 553</u> (V. KOHLER)</p> <p>* Claims 1,3,5 *</p> <p>----</p>	10	
			<b>CATEGORY OF CITED DOCUMENTS</b>
			<p>X: particularly relevant</p> <p>A: technological background</p> <p>O: non-written disclosure</p> <p>P: intermediate document</p> <p>T: theory or principle underlying the invention</p> <p>E: conflicting application</p> <p>D: document cited in the application</p> <p>L: citation for other reasons</p>
			<p>&amp;: member of the same patent family, corresponding document</p>
<p><input checked="" type="checkbox"/> The present search report has been drawn up for all claims</p>			
Place of search	Date of completion of the search	Examiner	
The Hague	08-11-1979		<b>WILLEKENS</b>